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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/214,453	10/25/99	LEADLAY	P

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EXAMINER	
KERR,K	
ART UNIT	PAPER NUMBER
1652	6

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Please find below and/or attached an Office communication concerning this application r proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No. 09/214,453	Applicant(s) LEADLAY ET AL.	
	Examiner Kathleen M Kerr	Art Unit 1652	

-- The MAILING DATE of this communication app ars on the cover sh et with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *22 June 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 24-43* is/are pending in the application.

4a) Of the above claim(s) *40-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 24-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Application Status

1. The instant Office action is in response to Applicants' election (Paper No. 15) which was in response to a written restriction requirement (Paper No. 13).

The instant application is a 371 filing of PCT/GB97/01819 filed on July 4, 1997. Two preliminary amendments were filed on October 25, 1999 with the filing of the instant application in the United States. Said amendments canceled Claims 4-23 from the international application and added Claims 24-43. Thus, Claims 1-3 and 24-43 are pending in the instant application.

Election

2. Applicant's election with traverse of the restriction of Groups I-III in Paper No. 15 is acknowledged. The traversal is on the ground(s) that the restriction is improper because DNA sequence and the encoded proteins cannot be restricted (as per Example 17 in M.P.E.P. § 1893.03(d)). This is not found persuasive because the Examiner has not restricted between DNA (Claims 1-3, 24-34, and 36) and encoded proteins (Claim 35) all of which are restricted to Group I according to lack of unity requirements; the polyketides of Claim 40 are not encoded (as this term is used in the art) by either the PKS genes or the PKS enzymes. The traversal is also on the ground(s) that the restriction is improper because an Examiner has previously determined that two Groups, not three as are found in the instant restriction requirement. This is not found persuasive because restriction according to U.S. restriction practice or international lack of unity practice is at the discretion of the Examiner (see 37 C.F.R. 1.499 in M.P.E.P. 1893.03(d)). The

Examiner did not hold a lack of unity in the international application; however, adequate reasoning for lack of unity has been set forth in the previous Office action.

The requirement is still deemed proper and is therefore made FINAL.

Priority

3. The instant application is granted the benefit of priority for the International Application No. PCT/GB97/01819 filed on July 4, 1997 which claims benefit of (1) U.S. Provisional Application No. 60/024,188 filed on August 19, 1996, (2) Great Britain foreign application 9614189.0 filed on July 5, 1996, and (3) Great Britain foreign application 971062.3 filed on May 28, 1997 as requested in the declaration. The Examiner notes that the requirements of national stage entry of the instant application had been completed (note assigned U.S. filing date) within 30 months of the earliest claimed priority date; the related international application includes both a search report and a preliminary examination report.

Information Disclosure Statement

4. The information disclosure statement filed on April 10, 2000 (Paper No. 8) has been reviewed, and its references have been considered as shown by the Examiner's initials next to each citation on the attached copy.

Drawings

5. The drawings are considered informal for the reasons detailed in the attached copy of PTO Form 948. Appropriate correction is required prior to allowance.

Compliance with the Sequence Rules

6. An amendment was filed on October 6, 2000 (Paper No. 11) containing a sequence listing in computer-readable form and paper copy. Said amendment has been entered but does not bring the instant application into full compliance with the sequence rules (see below). Since the sequence listing is adequate for examination purposes, the application is being examined prior to complete compliance.

7. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to **fully** comply with the requirements of 37 C.F.R. § 1.821 through 1.825; Applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990).

a. The following pages contain sequences without SEQ ID NO identifiers; appropriate correction to the sequence listing and specification is required: pages 26-30, 32, 35, 42, 44, 45, 48, 49, 51-53, 58, 61, 63, 73-75, 77, 79, 82, 83, 85, 86, 90, 91, 100, 101, 104, 105, 112, 117, and 118.

If the noted sequences are in the sequence listing as filed, Applicants must amend the specification to identify the sequences appropriately by SEQ ID NO. If the noted sequences are not in the sequence listing as filed, Applicants must provide (1) a substitute copy of the sequence listing in both computer readable form (CRF) and paper copy, (2) an amendment directing its entry into the specification, (3) a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. § 1.821 (e) or

1.821(f) or 1.821(g) or 1.821(b) or 1.825(d), and (4) any amendment to the specification to identify the sequences appropriately by SEQ ID NO.

Objections to the Specification

8. The specification is objected to for lacking continuity data in the first paragraph. The instant application claims the benefit of U.S. Provisional Application No. 60/024,188 filed on August 19, 1996; however, no citation is noted in the first paragraph. Appropriate amendment to the specification is required (see M.P.E.P. § 201.11).

9. The specification is objected to because it does not contain an abstract of the disclosure as required by 37 C.F.R. § 1.72(b). An abstract on a separate sheet is required.

10. In the specification, the Title is objected to for not completely describing the claimed subject matter being examined. A new, more aptly descriptive title is required. The Examiner suggests the following new title:
---Hybrid Polyketide Synthases Combining Heterologous Loading and Extender Modules---

11. The specification is objected to for lacking a section labeled "Brief Description of the Drawings", which section is found on page 27 of the specification. Appropriate amendment to include a title in this section in the specification is required. Also, this section describes Figures 33-34 but no such figures have been filed in the instant application (40 sheets of drawings have been filed). Also, apparent Figures 27 and 30 are unlabeled.

Claim Objections

12. Claim 3 is objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The requirements of an acyltransferase (AT) domain and an acyl carrier protein (ACP) domain are inherent in the art-recognized definition of "loading module" and, thus, do not further limit the subject matter of the parent claim.

13. Claim 24 is objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. From Applicants' remarks in Paper No. 15, the instant claim is intended to read on a hybrid PKS gene with an AT-ACP-KS loading module and a heterologous extender module, wherein the KS portion of the loading module is homologous to the extender module. Said KS portion cannot be heterologous (as required by the limitations of Claim 1) and homologous (as required by the limitations of Claim 24) at the same time. Thus, Claim 24 fails to properly further limit the subject matter of the parent claim. The Examiner suggests a new, independent claim to correct this defect.

14. Claim 32 is objected to for a typographical error; Claim 32 should depend from Claim 31 (not 11 as filed). Appropriate correction is required. The instant claim will be examined as if said amendment has been made.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claim 24 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 24 is wholly confusing. According the Applicants' remarks in Paper No. 15, the instant claim is intended to read on a hybrid PKS gene with an AT-ACP-KS loading module and a heterologous extender module, wherein the KS portion of the loading module is homologous to the extender module. Said KS portion cannot be heterologous (as required by the limitations of Claim 1) and homologous (as required by the limitations of Claim 24) at the same time. Moreover, the term "(only)", found in parentheses is confusing as to its intended meaning. Also, the term "the homologous extender module" (emphasis added) is unclear since it has no antecedent basis.

Additionally, the Examiner notes that, while Applicants' remarks are helpful in ascertaining the intending meaning, amendments to confusing claims are required for clarification.

Due to the wholly confusing nature of the instant claim, said claim will not be further treated on its merits.

16. Claim 27 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "an avr loading module" is unclear. Firstly, the abbreviation "avr" must

be defined upon its first appearance in the claims. Secondly, the instant specification describes one avr loading module while the term "an" indicates many; if a particular avr loading module is intended, the instant phrase should be ---the avr loading module---.

17. Claim 28 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 28 is wholly unclear. Neither the claim as filed nor Applicants' remarks in Paper No. 15 render the instant claim clear. The Examiner has carefully considered the definitions of natural and combinatorial modules provided in the instant specification; however, said definitions do not assist in the clarity of the claim.

Due to the wholly confusing nature of the instant claim, said claim will not be further treated on its merits.

18. Claim 29 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The words "nucleic acid" are confusing. It seems Applicants' intend to claim a gene according to claim 1 further comprising a nucleic acid **sequence** encoding a chain terminating enzyme other than a thioesterase; however, the instant claim as written is confusing in its intended meaning.

19. Claim 30 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 30 is wholly unclear as to its meaning as previously noted by the Examiner

in the Comments section in the Restriction Requirement (Paper No. 13). Applicants' have offered no clarification to assist the Examiner in the initial examination of the instant claim. Particularly, the phrases "leading to" and "natural unit" are unclear. In the art, extender modules produce (not lead to) polyketides products, which are compounds, not enzymes and/or proteins. Since the instant claim is drawn to a hybrid PKS gene, the phrase "natural unit" needs a reference (i.e., native to the extender module).

Due to the wholly confusing nature of the instant claim, said claim will not be further treated on its merits.

20. Claims 31-34 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The product claimed is not a "nucleic acid" as claimed, but is a "nucleic acid sequence" (emphasis added) since a single nucleic acid molecule (A, T, G, or C) cannot encode an entire protein.

21. Claims 32 and 34 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear whether the "natural activator gene" is required to be a part of the nucleic acid sequence claimed or not since the term "accompanied by" is not a term of art. The Examiner suggests the phrase "further comprising".

22. Claim 38 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as

the invention. The phrases "'donor' DNA" and "heterologous chromosomal PKS DNA" are unclear as to its meaning. Particularly, the phrase "heterologous chromosomal PKS DNA" is wholly unclear. The Examiner suggests removing the dependency on Claim 37 and amending the claim to be

---A method of producing a transformed organism comprising the steps of

(1) producing a plasmid comprising a gene according to claim 1 which is modified to be capable of homologous recombination with UNCLEAR and

(2) transforming an organism with said plasmid;

whereby said transformed organism is able to express a polyketides synthase encoded by said plasmid.---

Due to the wholly unclear nature of the instant claim, said claim cannot be further treated on its merits.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

23. Claim 29 is rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The instant claim requires a nucleic acid sequence encoding a chain terminating enzyme other than thioestersase; no such nucleic acid

sequence is described except using functional terms. To satisfy the written description aspect of 35 U.S.C. § 112, first paragraph, for a claimed genus of molecules, it must be clear that: (1) the identifying characteristics of the claimed molecules have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed. The specification does not disclose *any* representative species of any of the recited classes of possible nucleic acid sequences, with or without identifying characteristics such as structure. Therefore, claim 29, as written, fails to satisfy the written description requirement.

24. Claim 29 is rejected under 35 U.S.C. § 112, first paragraph, enablement, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The instant claim is drawn to a hybrid PKS gene comprising a nucleic acid sequence encoding s chain terminating enzyme other than a thioesterase. To identify and include such a nucleic acid sequence would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is

needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Chain terminating thioesterase (TE) domains in PKS genes are well known in the art as the enzymes which cleave the developed polyketide from the enzymes which produced it along the PKS enzyme complex. No other enzyme catalyzing such an activity is identified in the art, prior or post-filing, or in the specification. Applicants' have presented no guidance or working examples for the identification of such a nucleic acid sequence. Thus, the identification and use of such a product is wholly unpredictable.

25. Claims 37 and 39 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to transformed organisms and methods of using said organisms. To satisfy the written description aspect of 35 U.S.C. § 112, first paragraph, for a claimed genus of products (or methods of using said products), it must be clear that: (1) the identifying characteristics of the claimed products have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics

when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed. The specification does adequately describe transformed **microorganisms**, such as *Streptomyces* species, available for transformation using hybrid modular PKS genes. However, from the genus of microorganisms disclosed, one of skill in the art cannot predict the structure and/or function of the genus claimed due to the unpredictability of prokaryotic vs. eukaryotic organisms. Thus, the specification does fully describe, literally or representatively, the claimed genus in Claims 37 and 39.

26. Claim 39 is rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for using particular polyketides-producing microorganisms in the claimed methods, does not reasonably provide enablement for *all* organisms in the claimed methods. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The instant claim is drawn to methods of making polyketides using organisms transformed with genes encoding hybrid, modular (type I) polyketide synthases (PKSs). At the time of the invention, the ability to recombinantly produce polyketides by such a method was extremely limited as to the host organisms. As taught by Kao *et al.* (Science (1994) 265:509-512), modular PKSs are difficult to recombinantly express for the production of polyketides(see page 509, right column); however, polyketides can be produced via transformed PKS genes in recombinant microorganisms that natively produce polyketides, like *Streptomyces coelicolor*

CH999. To enable production of polyketides in **any** organism, one of skill in the art would be required to perform undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988) as noted above.

The instant specification uses *Saccharopolyspora erythraea* JC2 to recombinantly produce polyketides, said JC2 strain is a natively-producing polyketide strain with its native PKS genes deleted (see specification, page 23). All other examples of host organisms in the specification are *S. coelicolor*, as taught by Kao *et al.* and which natively produces actinorhodin, *S. erythraea* which natively produces erythromycins, or *Streptomyces avermitilis* which natively produces avermectin. Thus, all examples of the claimed genus taught in the instant specification are drawn to using microorganisms which natively produce polyketides. Applicants present no guidance of direction for the purpose of using other organisms. The state of the prior art is such that using other organisms is wrought with difficulties and wholly unpredictable. Thus, the instant claim is not enabled to the full extent of its scope by virtue of the specification or the prior art at the time of the invention.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

27. Claims 1, 31-37, and 39 are rejected under 35 U.S.C. § 102(e) as being anticipated by Khosla *et al.* (USPN 5,962,290 effective filing date of June 7, 1995 via divisional parent USPN 5,712,146). The instant claims are drawn to (1) nucleic acid sequences encoding hybrid modular PKS genes operably linked to the *act I* promoter from *S. coelicolor* in the presence of its natural activator gene (*actII-orf4*), (2) hybrid PKS enzymes as encoded by said nucleic acid sequences, (3) vectors comprising said nucleic acid sequences, (4) transformed microorganisms comprising said nucleic acid sequences, and (5) methods of making polyketides using said microorganisms.

Khosla *et al.* teach a "DNA molecule which comprises a recombinant expression system for production of a hybrid modular (Type I) PKS...wherein said activities [KS, AT, ACP, etc.] are derived from at least two different modular PKS" (see Claim 10). Khosla *et al.* teach examples of genes for use in hybrid nodular PKS clusters such as erythromycin, tylosin, carbomycin, spiramycin, avermectin, and candicidin (see column 14, lines 26-35). Khosla *et al.* further teach said DNA molecule operably linked to an actinorhodin (act) promoter (see Claim 17) in the presence of "actII-ORF4, an activator gene, which is required for transcription from these [actI/actIII] promoters" (see column 19, lines 38-40). Khosla *et al.* further teach host cells containing said DNAs (see Claims 11 and 18), the production of which host cells inherently requires the use of vectors. Khosla *et al.* also teach methods of making modular PKSs as encoded by said DNA molecules (see Claims 12 and 19), the product of which methods is the claimed hybrid PKS enzymes of Applicants' Claim 35. Said methods of making modular PKSs are inherently also methods of making polyketides, as claimed in Applicants' Claim 39. Moreover, Khosla *et al.* teach that their methods are useful for "efficiently producing both new and known polyketides, using recombinant technology" (see column 3, lines 7-10). Lastly,

Khosla *et al.* is replete with teachings of hybrid, (type I) modular PKS genes and enzymes (see for example, column 4, lines 44-65, column 9, lines 38-50, column 13, lines 53-58, and column 25, lines 24-40).

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

28. Claims 2, 3, 25, and 26 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Khosla *et al.* The instant claims are drawn to nucleic acid sequences encoding hybrid modular PKS genes wherein (1) said nucleic acid sequences include at least a loading domain and an extender domain, (2) said loading and extender domains are heterologous, (3) said loading domain initiates polyketide synthesis with a starter unit different from a starter unit normally utilized by said extender domain, and (4) said loading domain is capable of using many different starter units.

Khosla *et al.* teach as describe above. Khosla *et al.* further teach that the DEBS loading domain can use a multiplicity of starter units (see column 42, lines 39-41). Khosla *et al.* do not specifically teach an embodiment of a hybrid PKS gene that is the DEBS PKS gene cluster, a cluster which has a loading domain using more than one starter unit, with a substituted, corresponding domain from, for example, the modular PKS gene cluster for spiramycin. Such a PKS gene meets all the limitations of the instant claims.

It would have been obvious to one of ordinary skill in the art to produce the claimed invention because Khosla *et al.* particularly teach all domain combinations for hybrid PKS gene clusters using the noted modular PKS genes. One would have been motivated to produce such a hybrid PKS gene, specifically using the DEBS loading module, in view of the teachings of Khosla *et al.* concerning the relaxed specificity of the DEBS loader particularly since a more relaxed specificity can give rise to a greater variety of polyketides produce – the utility of the entire Khosla *et al.* disclosure.

29. Claim 27 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Khosla *et al.* in view of Kao *et al.* (Science (1994) 265:509-512). The instant claim is drawn to nucleic acid sequences encoding hybrid modular PKS genes wherein (1) said nucleic acid sequences include at least an avr loading domain and an extender domain and (2) said loading and extender domains are heterologous.

Khosla *et al.* teach as describe above. Khosla *et al.* also teach that " modular PKSs...[use] a wider range of primer units...[and] have relaxed specificity for their starter units" (see column 25, lines 24-37). Khosla *et al.* do not teach using the avermectin loading domain in the disclosed hybrid PKS genes.

Kao *et al.* teach the relaxed specificity of the starter units of the DEBS PKS genes as well as of the avermectin PKS genes (see page 511, left column).

It would have been obvious to one of ordinary skill in the art to combine the teachings of Khosla *et al.* and Kao *et al.* to produce the claimed invention because the main focus of the teachings of Khosla *et al.* is the achievement of diversity in polyketide production using hybrid PKS genes and both DEBS and avermectin loading domains are known to add diversity by virtue

of their relaxed starter unit specificities. One would have been motivated to produce the specific embodiment of using an avr loading domain to produce a more diversity population of polyketides for use as possible therapeutics as taught by Khosla *et al.* Moreover, one would have had a reasonable expectation of success that the claimed combination of domains would function together in view of the teachings of Khosla*et al.* and because the combination of modular PKS genes in a hybrid PKS has been shown to produce functional PKSs.

Conclusion

30. Claims 1-3 and 24-39 are not allowed for the reasons identified in the numbered sections of this Office action. Claims 24, 28, 30, and 38 (confusing, 112/2nd issues) were not considered for art rejections due to their total lack of clarity which precluded an effective search of the prior art. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. . Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 3080196.

KMK
September 10, 2001

PONNATHAPU ACHUTAMURTHY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600